in the structural variations of the human genome. This evidence includes the sheer number of repetitive elements, the de novo transposition/insertion/mutation rates, the fact that similar elements (e.g., *Alu-Alu*, LINE-LINE) can act as substrates for homologous recombination and can generate CNVs by nonallelic homologous recombination (NAHR), and that such elements can provide microhomology for priming polymerase extension during template switching in replication-based mechanisms (Zhang et al., 2009).

The junk DNA has come out of the closet or garage (depending on your favorite euphemism) and begun to reveal its immense value to genome evolution and human biology. It has certainly been fascinating to witness the transformation of human repetitive sequences from a nuisance that needs to be quenched during hybridizations to a central player in structural variation, arguably the most common form of genetic variation in humans and one that figures prominently in evolution and disease.

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Alzheimer's Disease Neurons Fail the Acid Test

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Mutations in the *presenilin* genes are the most common cause of familial forms of Alzheimer's disease. Although it is well known for its role in the generation of amyloid peptide, Lee et al. (2010) now report that presenilin 1 deficiency also impacts maturation of the lysosomal proton pump, affecting autophagocytosis and protein turnover.

Although amyloid plaques and neurofibrillary tangles are the classic hallmarks of Alzheimer's disease (AD) pathology, AD is also characterized by endosomal/lysosomal abnormalities including the aberrant accumulation of subcellular structures involved in autophagy (the degradation of long-lived organelles and macromolecules), such as autophagosomes, autolysosomes, and lysosomal dense bodies. Multiple lines of evidence now suggest a potential link between AD and autophagy. These include reports that *presenilin 1*, the gene most frequently mutated in familial forms of AD, has a role in autophagocytosis or may have a more general function in subcellular membrane trafficking (Esselens et al., 2004; Wilson et al., 2004; Sannerud and Annaert, 2009). In addition, disruption of the autophagy pathway promotes the deposition of amyloid plaques and accelerates neuronal loss (Pickford et al., 2008; Tooze and Schiavo, 2008).

In findings presented in this issue, Lee et al. (2010) strengthen this emerging connection between AD and autophagy and propose a mechanism that contributes to autophagosome accumulation observed in the disease. In normal cells, autophagosomes fuse with acidified lysosomes to promote the degradation of the autophagosome's contents. Lee et al. now report that disease-causing mutations in presenilin 1 impair the acidification of lysosomes, thereby interfering with the subsequent autophagosome clearance (Figure 1). Given that one of the signatures of neurodegenerative disorders is accumulation of aggregates of misfolded protein, decreased turnover of protein (as observed in the current experiments) might contribute to the disease process. These provocative and potentially controversial observations come amidst growing interest in molecular pathways that act in parallel (or possibly intersect) with the classical amyloid cascade.

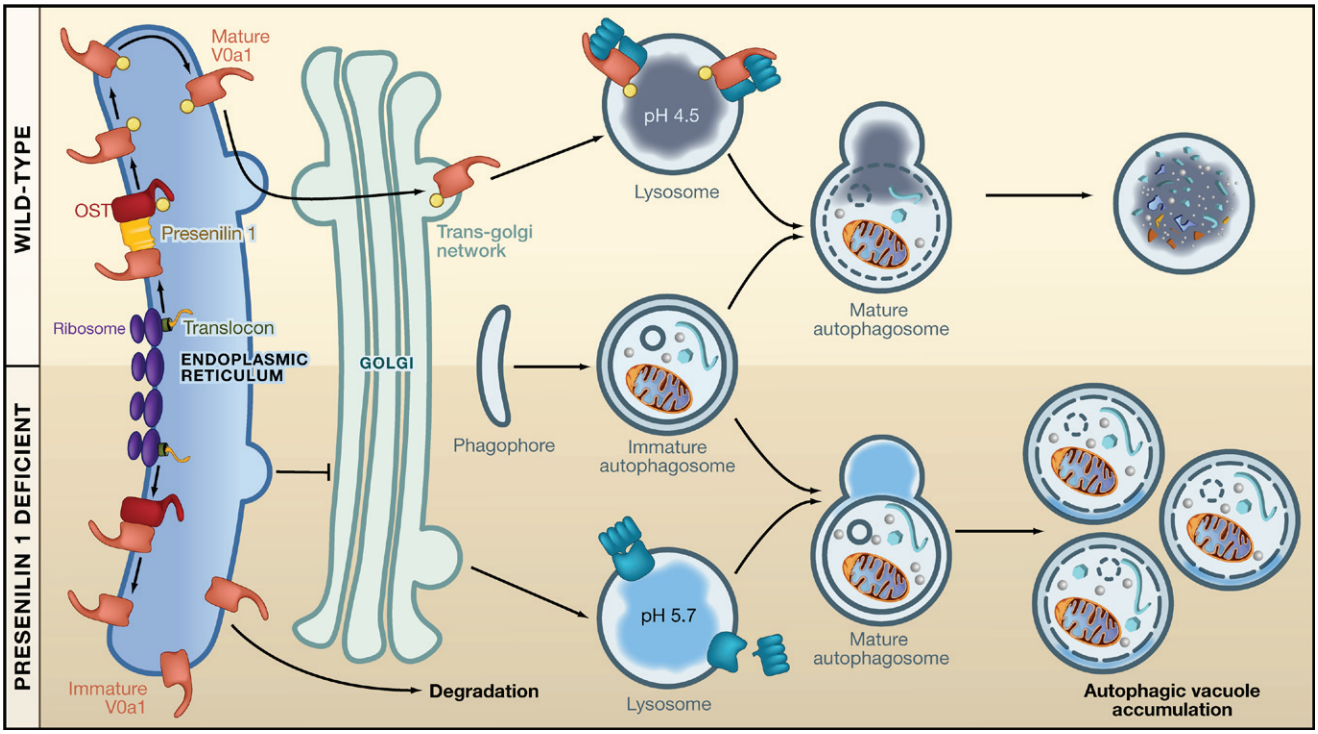

Figure 1. Presenilin 1 and Autophagosome Clearance

Depicted is a model explaining the role of presenilin 1 in the maturation and transport of the V0a1 subunit of the v-ATPase. In wild-type cells, presenilin 1 mediates the posttranslational addition of a single N-glycan to the immature V0a1 subunit through interaction with the oligosaccharyltransferase (OST) complex and the translocon. Glycosylated V0a1 traffics via the Golgi complex to the lysosome where it contributes to a functional v-ATPase, which is required for acidification of lysosomes. Deficiency of presenilin 1 prevents glycosylation, stalling immature V0a1 in the endoplasmic reticulum, therefore impairing v-ATPase assembly and resulting in decreased lysosomal acidification. This in turn prevents autophagosome clearance during macroautophagy causing autophagic vacuoles to accumulate (figure concept provided by S. Sannerud).

Presenilins are best known for their catalytic function in the γ-secretase complex (Wakabayashi and De Strooper, 2008). Disruption of this function by genetic or pharmacological inactivation interferes with the proteolytic processing of many proteins including notch (critical for embryonic development), cadherins, and amyloid precursor protein (APP). It is the processing of APP to amyloid peptide that is usually considered the main contribution of presenilin 1 to the pathogenesis of AD. To circumvent embryonic lethal notch phenotypes of *presenilin 1* knockout mice, Lee et al. examine conditional knockout mice and mice with a hypomorphic allele. The authors also examine fibroblasts from familial AD patients and observe a similar impairment of lysosomal acidification. Given that the familial AD patients have a wild-type allele, in addition to a mutant allele, it is especially remarkable that fibroblasts from these individuals mirror the cellular phenotypes observed in the mutant mice. Although the mutations in *presenilin 1* act in a genetically dominant manner, most lead to a loss of function in biochemical assays (Wakabayashi and De Strooper, 2008), and the data therefore suggest that the acidification defects observed are extremely sensitive to small alterations in the function of presenilin 1.

To explain these phenomena, the authors propose an intriguing model that encompasses most of the observations in the paper. In brief, they suggest that presenilin 1 is involved in the maturation of the V0a1 subunit of the bimodular v-type H^+-ATPase proton pump that acidifies the lysosome. The authors provide evidence that this subunit, which appears as a glycosylated 120 kDa band in wild-type cells, migrates as an unglycosylated 100 kDa precursor in cells lacking presenilin 1, and that due to the absence of glycosylation the immature V0a1 subunit remains stuck in the endoplasmic reticulum. Based on coimmunoprecipitation of presenilin 1 with this immature V0a1 protein, and with subunits of the translocon and the oligosaccharyltransferase complex (Ruiz-Canada et al., 2009), the authors make the bold suggestion that presenilin 1 presents the V0a1 subunit to the oligosaccharyltransferase that mediates N-glycan addition. Hence, in the absence of presenilin 1, N-glycosylation and transport of the V0a1 subunit do not occur.

Several questions remain to be addressed before considering this model as established. For instance, the oligosaccharyltransferase adds Endo H glycosidase-sensitive oligosaccharides to nascent proteins, whereas complex modifications occur later in the different Golgi compartments. Thus, it remains puzzling that no such Endo H-sensitive V0a1 intermediate was identified in wild-type cells. Also the question of specificity remains unaddressed: three other V0a subunits are known (Marshansky and Futai, 2008), but it seems very unlikely that they are all equally affected by presenilin 1. Indeed, this would lead to extensive depletion of functional proton pumps in cells deficient in presenilin 1 and much more severe

phenotypes than the ones observed. V0a1 subunits are implicated in vesicle fusion independent of their role in acidification (Marshansky and Futai, 2008), and it might be interesting to study that aspect in more depth. Finally, full-length presenilin 1, present in low amounts in the endoplasmic reticulum, is proposed to act as a Ca^{2+}-leak channel (Tu et al., 2006), and it is unclear how the new proposed function relates to this previous one.

The new work underscores the importance of presenilin 1 function in the endoplasmic reticulum and confirms its role in subcellular trafficking, in particular in the autophagocytic/lysosomal pathways. Taking these intriguing observations as a starting point, further in-depth exploration of the precise mechanism will ultimately result in a better understanding of the myriad functions of presenilins in health and disease.

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D'oh! Genes and Environment Cause Crohn's Disease

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Information obtained from genome-wide association studies has cracked open the biology of common chronic diseases by identifying genes that predispose individuals to these disorders. Cadwell et al. (2010) now demonstrate that a viral infection, a toxic insult to the gut, commensal bacteria, and a Crohn's disease susceptibility gene collude to cause inflammatory disease in the mouse gut.

A revolution is occurring in our understanding of the genetic basis of common chronic diseases such as arthritis, Crohn's disease, and cancer. Genome-wide association studies (GWAS) are identifying a plethora of common sequence variants of genes and of putative regulatory regions in or near genes that predispose an individual to developing a particular disease. This flood of new information is made possible by dramatic improvements in the genotyping of DNA polymorphisms across the human genome, increased levels of statistical rigor during the interpretation of results, and the large-scale collection of clinical resources. Nevertheless, doubts concerning the value of GWAS have arisen because in many cases a particular polymorphism only slightly increases an individual's risk for developing that disorder. Hence, some researchers ask, how can such a small genetic effect provide useful insights into the mechanisms of the disease? However, more pertinent questions are, which particular genes mapped by GWAS are involved in the etiology or cause of the disease and how do these genes act?

One common disorder for which GWAS have been spectacularly successful is a severe form of gut inflammation called Crohn's disease. GWAS of Crohn's disease patients provided the first clues that alterations in the expression and activities of genes known to function in autophagy (i.e., the pathway that degrades intracellular components, including pathogens) may predispose individuals to inflammation of the small intestine (Wellcome Trust Case Control Consortium, 2007). Two earlier studies, one by Cadwell et al. (2008) and another by Saitoh et al. (2008), took